REMARKS

The Office Action

Claims 1-29 were pending. Claims 22-29 have been withdrawn in response to a restriction requirement. Claims 1-21 stand rejected under 35 U.S.C § 112 second paragraph as being indefinite. Claims 1-3, 7, 11-12, 15-19, and 20-21 stand rejected under 35 U.S.C. § 102(e) as being anticipated by DeFrees et al. (U.S. Patent Application Publication No. 2004/0082026; "DeFrees"). Claims 4-6 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over DeFrees in view of Monkarsh et al. (*Anal. Biochem* (1997) 247: 434-440; "Monkarsh") and Shadle et al. (U.S. Patent No. 4,847,325; "Shadle"). Claims 13-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over DeFrees in view of Shadle. Claims 1-21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Smith et al. (*Mol. Cell. Biol.* (1983) 3:2156-2165; "Smith"), in view of Monkarsh, Shadle, and Francis (*Focus on Growth Factors* (1992) 3:4-10). Applicants address each of these rejections below.

Amendments to the Specification

Applicants have amended the specification to capitalize the trademark names WELLFERON, ALFERON, SUMIFERON, MULIFERON, ROFERON-A, INTRON-A, BEROFOR ALPHA 2, and INFERGEN, as required by the Office. Applicants note that the generic terminology ("natural interferon") for these trademark names is in the paragraph on page 4, lines 4-22 of the specification as filed.

Amendments to the Claims

Claim 1 has been amended to include the limitations of claim 4, with the exception of the term "pegylated." Claims 4 and 8 have been canceled. Claims 5 and 6, which originally depended from claim 4, have been amended to depend from claim 3. Similarly, claims 9 and 10, which originally depended from claim 8, have been amended to depend

from claim 7. Claims 16 and 17 have been amended for purposes of clarity.

The present amendments were made solely to expedite prosecution, and applicants reserve the right to pursue any cancelled subject matter in this or in a continuing application. No new matter has been added.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-21 stand rejected as being indefinite. According to the Office, the claims fail to "particularly point out and distinctly claim the subject matter which applicants regards as the invention. The metes and bounds of the term "asialo-interferon" are not clear." Applicants disagree, and point out that the language of the claim, read in light of the specification, is sufficiently clear to meet the standard set by 35 U.S.C § 112, second paragraph.

In particular, applicants' specification clearly defines the term "asialo-interferon" (page 5, line 24 to page 6, line14):

> By "asialo-interferon" is meant a glycosylated interferon lacking a terminal sialic group that is present in the native glycosylated interferon. Removal of the terminal sialic acid residue exposes the underlying galactose moiety. It is the terminal galactose that is recognized by the asialoglycoprotein receptor. Preferably, asialo-interferon contains at least 50%, 70%, 80%, 90%, or even 95% of the carbohydrate moieties present in the native interferon. Most preferably, asialo-interferon lacks only the terminal sialic acid residue. Asialo-interferons can be produced by removing one or more sialic acid groups from a glycosylated interferon, such as interferon-α, -β, or -γ. This removal may be accomplished, for example, by mild acid hydrolysis, or treatment of native glycosylated interferon, such as interferon-α, -β, or -γ, with purified neuroaminidase. For interferons containing more than one sugar chain, selective desialylation may be accomplished using specific neuroaminidase (sialidase) enzymes. Specifically excluded by this definition are completely deglycosylated interferons, including interferons that are typically produced by prokaryotic cells and interferons produced by eukaryotic cells and enzymatically or chemically deglycosylated. Of course, because the goal of removing the sialic acid residue is to create a glycosylated interferon having at

> least one terminal galactose residue on an oligosaccharide chain, a terminal galactose residue may be engineered by any other appropriate means including, for example, covalently attaching an oligosaccharide to a deglycosylated interferon.

Given this description, one skilled in the art would readily understand the meaning of the term "asialo-interferon" to mean a glycosylated interferon lacking a terminal sialic group, as defined on page 5, lines 24-25. The Office cites references (Marshal et al., *Biol. Chem.* (2001) 382:151-159; Altmann et al., *Glycoconjugate* (1999) 16:109-123; Sugyiami et al., *Eur. J. Biochem.* (1993) 217:921-927; Goochee et al., *Bio/Technology* (1991) 9:1347-1355) to show that not all native interferons are sialylated. However, one skilled in the art would understand the reference to "native glycosylated interferons" on page 5 to be purely illustrative. As such, this description "reasonably apprises those skilled in the art" of the scope of the present claims. See, for example, *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d 870, 27 U.S.P.Q.2d 1123 (Fed. Cir. 1993) ("If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more...The degree of precision necessary for adequate claims is a function of the nature of the subject matter."). Reconsideration on this point is requested.

Rejections under 35 U.S.C. § 102

Claims 1-3, 7, 11-12, 15-19, and 20-21 stand rejected as being anticipated by DeFrees. The Office states (Office action, page 5):

> DeFrees teaches pegylation of asialo-IFN molecules, including α and β (see paragraphs 1683-1701). Specifically PEG of 10 kDa and 20 kDa is taught (paragraph 1689). Thus DeFrees anticipates the limitations of claims 1-3 of the instant application. DeFrees also teaches modification of human IFN α, β, and γ polypeptides (paragraph 1188), and therefore meets the limitations of claims 11-12 of the instant application. Finally, DeFrees teaches pharmaceutical compositions of the modified IFN polypeptides (paragraph 0117). Taken together, the teaching of

> DeFrees meet the limitations of claims 15-18 and 20-21 of the instant application, which are drawn to pharmaceutical compositions of pegylated human asialo-IFN molecules…DeFrees also teaches the use of polyvinyl-pyrrolidone (PVP) as a water-soluble polymer than can be used to modify IFN polypeptides (paragraph 0734), and pharmaceutical compositions of modified IFN polypeptides (see above), thus meeting the limitations of claims 7 and 19 of the instant application.

Claim 1, as amended, recites:

> 1. A modified asialo-interferon, comprising an asialo-interferon that is conjugated to a water-soluble polymer having an average molecular weight of approximately 1,000 to 60,000 daltons, wherein said water-soluble polymer is conjugated to said asialo-interferon at a cysteine, lysine, serine, threonine, tyrosine, aspartic acid, or glutamic acid residue; at a C-terminal carboxyl; or at an N-terminal amine.

DeFrees does not teach a water-soluble polymer conjugated to an asialo-interferon at specific amino acid residues as presently claimed. Indeed, as stated by the Office (page 6), "DeFrees…is silent regarding pegylation of any specific amino acid residue." Accordingly, DeFrees does not anticipate claim 1 as amended, and the rejection may be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 4-6 stand rejected as being unpatentable over DeFrees in view of Monkarsh and Shadle. Claims 13-14 stand rejected as being unpatentable over DeFrees in view of Shadle. Claims 1-21 stand rejected as being unpatentable over Smith in view of Monkarsh, Shadle, and Francis. For the following reasons, each of these rejections should be withdrawn.

Claims 4 to 6

Claims 4 to 6 stand rejected as being unpatentable over DeFrees in view of Monkarsh and Shadle. Claim 4 has been canceled and claims 5 and 6 have been amended to depend from claim 3. Claims 3, 5 and 6 read as follows:

> 3. The modified asialo-interferon of claim 1, wherein said modified asialo-interferon is a pegylated asialo-interferon.
>
> 5. The modified asialo-interferon of ~~claim 4~~ claim 3, wherein said pegylated asialo-interferon is pegylated at a cysteine residue.
>
> 6. The modified asialo-interferon of ~~claim 4~~ claim 3, wherein said pegylated asialo-interferon is pegylated at a lysine residue.

As noted in the specification, the term "asialo-interferon," as used in claim 1, refers to a "glycosylated interferon lacking a terminal sialic group" (page 5, lines 24-25). In this regard, applicants point out that DeFrees teaches that "peptides whose glycans ***do not contain terminal sialic acid residues are rapidly removed from the circulation by the liver, an event which negates any potential therapeutic benefit of the peptide*** (column 1, paragraph 0003, emphasis added)." Given this teaching, DeFrees plainly does not teach or suggest applicants' claimed invention.

Clearly, DeFrees discourages one skilled in the art from applicants' claimed compound. The DeFrees teaching would lead a person of ordinary skill, upon reading the reference, in a direction divergent from the path that was taken by applicants. The skilled worker would not be led to construct the claimed asialo-interferons. For this reason alone, the obviousness rejection in this case must be withdrawn. See, for example, *In re Haruna*, 249 F.3d 1327, 1335, 58 U.S.P.Q.2d 1517, 1522 (Fed. Cir. 2001) ("A prima facie case of obviousness can be rebutted if the applicant...can show 'that the art in any material respect taught away' from the claimed invention....*A reference may be said to teach away when a person of ordinary skill, upon reading the reference,...would be led in*

a direction divergent from the path that was taken by the applicant.") (emphasis added) (citations omitted).

Moreover, while Monkarsh does describe pegylated interferons, Monkarsh does not teach, suggest, or motivate the skilled worker to generate pegylated *asialo*-interferons. Further, Shadle describes the "modification of IL-2, IFN-β and immunotoxins with PEG through cysteine residues of a polypeptide (column 3, lines 16-18)." However, Shadle, like Monkarsh, does not teach, suggest, or motivate the skilled worker to generate pegylated asialo-interferons.

Given the specific teaching of DeFrees, it is hard to imagine a person skilled in the art being motivated to combine DeFrees, Monkarsh, and Shadle to arrive at the presently claimed invention. Thus, applicants respectfully request that the rejection of claims 4 to 6 be withdrawn.

Claims 13 and 14

Claims 13 and 14 stand rejected as being unpatentable over DeFrees in view of Shadle. As discussed above, neither DeFrees nor Shadle, alone or in combination, render the claimed invention obvious. The rejection to claims 13 and 14 may be withdrawn.

Claims 1 to 21

Claims 1 to 21 stand rejected as being unpatentable over Smith in view of Monkarsh, Shadle and Francis. Applicants disagree.

In connection with an obviousness analysis, the Federal Circuit has further stated:

> "[V]irtually all [inventions] are combinations of old elements." Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue.

In re Rouffet, 149 F.3d 1350, 1357-58, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998) (internal citations omitted).

> "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure."

In re Dow Chem. Co., 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

As the Federal Circuit has observed (emphasis added):

> A critical step in analyzing the patentability of claims pursuant to section 103(a) is ***casting the mind back to the time of invention***, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. . . . ***Most if not all inventions arise from a combination of old elements***. . . . Thus, every element of a claimed invention may often be found in the prior art. . . . However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. . . . Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.

In re Kotzab, 217 F.3d 1365, 1369-70, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000) (citations omitted) (emphasis added).

Moreover, the evidence of a suggestion, teaching, or motivation to combine "***must be clear and particular*** (emphasis added)." *Dembiczak*, 175 F.3d at 999, 50 U.S.P.Q.2d at 1617. "Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." *Monarch Knitting Mach. Corp. v. Sulzer Morat GMBH*, 139 F.3d 877, 881, 45 U.S.P.Q.2d 1977, 1981 (Fed. Cir. 1998). Thus, even if the Office identifies every element of a claimed invention in the prior art, this alone is insufficient to negate patentability. Otherwise, "rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention." *Rouffet*, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d

1453, 1457 (Fed. Cir. 1998). To avoid hindsight based on the invention to defeat patentability of the invention, the Federal Circuit requires the Office to show a motivation to combine the references that create the case of obviousness. *Id.* That is, "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and ***with no knowledge of the claimed invention***, would select the elements from the cited prior art references for combination in the manner claimed." *Id* at 1357, 1458 (emphasis added). The Office has failed to show a *prima facie* case of obviousness and the rejections of claims 1 to 21 in view of the Smith, Monkash, Shadle, and Francis prior art combination should therefore be withdrawn.

As motivation for combining the cited references, the Office states that:

> One of ordinary skill in the art would be motivated to combine the teachings of Smith et al with those of Monkarsh et al, Shadle et al, and Francis to practice the claimed invention. Smith et al provides the skilled artisan with a method of producing an asialo-IFN, and Monkarsh et al and Shadle et al provides the skilled artisan the motivation to modify the asialo-IFN via pegylation, while Francis provides the motivation to modify the asialo-IFN via pvpylation. Furthermore, Monkarsh et al and Shadle et al provide the motivation for modification on lysine or cystiene residues, respectively, and Shadle et al also provides the motivation for the incorporation of additional cystein residues. Finally, Smith et al., by teaching that IFN-β has antiviral, antiproliferative, and antitumor properties, would provide the skilled artisan the motivation to incorporate the modified asialo-IFN in a pharmaceutical composition. Therefore, one of ordinary skill in the art would not only have the motivation to combine the teachings of Smith et al with those of Monkarsh et al, Shadle et al, and Francis, to practice the claimed invention, but also a reasonable expectation of success in producing the claimed modified asialo-IFN.

There is, however, nothing in the references of record that provides any basis for modifying Smith's asialo-interferon to arrive at the currently claimed compounds. The Office's analysis amounts to merely an invitation to experiment. First, the Office's statement that "Smith et al provides the skilled artisan with a method of producing an

asialo-IFN, and Monkarsh et al and Shadle et al provides the skilled artisan the motivation to modify the asialo-IFN via pegylation, while Francis provides the motivation to modify the asialo-IFN via pvpylation" is plainly predicated on an improper "obvious to try" standard. Smith does not even mention modification of an asialo-interferon, much less discuss modification of an asialo-interferon with a water-soluble polymer, such as PEG. Monkarsh or Shadle, alone or in combination, fail to teach or suggest a pegylated asialo-interferon as claimed. Francis not only fails to teach or suggest a pegylated asialo-interferon, but in fact fails to teach or suggest interferons at all. It is insufficient for the Office to say that one skilled in the art might find it "obvious to try" combining the Smith, Monkarsh, Shadle, and Francis references.

Furthermore, as discussed above, DeFrees teaches away from using an asialo-interferon. In view of the teachings of DeFrees, a skilled artisan would not only lack motivation to combine Smith with any of Monkarsh, Shadle, or Francis, but in fact would be discouraged from doing so.

As the Federal Circuit has held, an obvious to try situation does not render a claim "obvious" within the meaning of section 103. ("An invention is obvious to try rather than obvious within the meaning of § 103 ""where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful."" *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989) (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)).)

The Smith, Monkash, Shadle, and Francis prior art combination is not the type of "clear and particular" motivation required by the Federal Circuit. *In re Dembiczak*, 175 F.3d at 999. Without motivation for the combination of references, no *prima facie* case of obviousness can exist, and the § 103 rejection on this basis must be withdrawn.

As the references do not provide motivation to combine to arrive at the presently claimed invention, Applicants respectfully request that the rejection of claims 1to 21 be withdrawn.

CONCLUSION

Applicant submits that the claims are in condition for allowance and such action is respectfully requested. Enclosed is a petition to extend the period for replying for 3 months, to and including September 15, 2006.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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